Remarks/Arguments

Claims 25 and 26 are withdrawn. Claim 1 has been amended. Subsequent to the entry of the present amendment, claims 1-25 and 27-29 are pending and at issue. Reconsideration of the application is respectfully requested in view of the following remarks.

Rejections under 35 U.S.C. §103

The Examiner maintains the rejection of claims 1-24 and 27-29 under 35 U.S.C. §103(a) as allegedly obvious over Merrified *et al.* (PCT Publication No. WO 00/37169) in view of Manning *et al.* (U.S. Patent No. 5,770,559). Applicants respectively traverse this rejection.

The Office Action states in relation to Merrified *et al.* that "the instant claims never specify at which point the substance of interest precipitates, whether it does so at the point of contact between the solvent and anti-solvent streams, or at a point further downstream". We respectfully disagree.

Firstly, we respectfully submit that the Examiner has misconstrued the claimed method in light of Merrified *et al.* Claim 1 (as filed) of the present application claims

> *"A method for forming fine particles of a substance, the method including contacting a non-gaseous fluid containing the substance with a dense gas to expand the fluid, the dense gas including (a) an anti-solvent and (b) a modifying agent which modifies the polarity of the anti-solvent."*

Since the claims of a patent specification are addressed to one of ordinary skill in the art, we submit that such a person would have no difficulty in interpreting the language of this claim to understand that the substance of interest precipitates as a result of contact between the solvent and anti-solvent streams. The phrase "...to expand the fluid..." would be understood to mean that the substance of interest is precipitated by that contacting. The act of expanding the fluid

causes the solubility of the substance of interest in the fluid to decrease, causing the substance of interest to precipitate.

Put another way, the non-gaseous fluid contains the substance of interest in solution. It is believed that in the process of the present invention, when the non-gaseous fluid comes into contact with the dense gas, the non-gaseous fluid in which the substance is dissolved is expanded, resulting in a drop in the solubility of the substance of interest in the non-gaseous fluid. This drop in solubility causes the substance of interest to precipitate from solution. The contacting of the dense gas with the non-gaseous fluid results in the precipitation. On reading claim 1 as filed, we submit that one of ordinary skill in the art would immediately interpret the term "expand" to mean that the substance of interest would be precipitated upon contacting, i.e., at the point where the non-gaseous fluid containing the substance contacts the dense gas, in accordance with the process description outlined above.

However, while we disagree with the Examiner on this point, claim 1 has been amended to include explicit language that the fine particles of a substance are formed upon contacting a non-gaseous fluid containing the substance with a dense gas.

Secondly, we contend that §103 is not applicable to the pending claims. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation to modify a reference or to combine the teachings of multiple references. Second, there must be a reasonable expectation of success. Third, the prior art must teach or suggest all of the recited claim limitations. Of course, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure.

Motivation to combine documents

We submit that it is not at all obvious that one of ordinary skill in the art would be motivated to combine the disclosures of Merrified *et al.* and Manning *et al.* We submit that it would be extremely unlikely that one of ordinary skill in the art would be motivated to combine two disclosures that describe processes that are quite different. Merrified *et al.* describes a process and apparatus for the production of particles of a material in which a stream of a dispersion of the material in a solvent and a stream of the compressible fluid anti-solvent substance are mixed under conditions such that the substance is in a compressed fluid anti-solvent state. The precipitation of the material does not occur at the point of mixing, however. After the two streams are mixed, the mixture flows along a conduit towards an orifice from which it flows into a downstream region, where precipitation occurs upon decompression of the anti-solvent substance (see, for example, page 3, line 27 to page 4, line 7 of Merrified *et al.*).

Manning *et al.*, on the other hand, relates to a method of preparing a true, homogeneous solution of a pharmaceutical substance dissolved in an organic solvent in which the pharmaceutical substance is not normally soluble using amphiphilic reagents. This solution may then be further processed to prepare pharmaceutical powders using, for example, a gas anti-solvent process.

The inventions disclosed in Merrified *et al.* and Manning *et al.* are, therefore, directed to solving different problems. The invention of Merrified *et al.* is directed to an alternative process for the production of particles, whereas the invention in Manning *et al.* is directed to a method of preparing a true, homogeneous solution of a pharmaceutical substance (the substance may then be precipitated using an antisolvent process). Since the documents are directed to solving different problems, we therefore submit that there is no motivation in either Merrified *et al.* of Manning *et al.* to modify either reference or to combine the documents.

Reasonable expectation of success

The Office Action states that "regardless of how the Applicant characterizes the disclosure of the Merrified *et al.* patent in terms of the selection of an anti-solvent, it does not change the fact that anti-solvents such as ethane and ethylene, which read on the instance claims, are disclosed within the prior art" and "the prior art remains relevant for all that it contains, not just preferred embodiments, such that non-preferred and alternative embodiments disclosed within the prior art can be properly applied against the instant claims".

We point out that Merrified *et al.* was cited by the Examiner in relation to obviousness (it is correctly not relied on for novelty as it does not meet the 35 U.S.C. §102 requirements), and as such the preferred choice of antisolvents is a relevant consideration. In Merrified *et al.*, carbon dioxide is the preferred antisolvent and all of the examples in the document use carbon dioxide as the antisolvent. There is no teaching in the document as to how the process described in the document would perform with a different antisolvent. This consideration is particularly important in relation to the present application because biologically active substances are very sensitive to changes in pH and the solvent environment. Carbon dioxide has an effect on the pH of an aqueous solution due to carbonic acid formulation, so the preferred process of the Merrified *et al.* document may have an adverse effect on the integrity of the substance of interest. This problem is not foreshadowed or contemplated by Merrified. Therefore, for at least the reasons stated above, we submit that modifying the teachings of Merrified *et al.* does not provide one of ordinary skill in the art with any reasonable expectation of success.

In relation to Manning *et al.*, we submit that modifying the teaching in the document would not provide any reasonable expectation of success. The solubilisation process described in the document requires a hydrophobic–ion pair complex (between the pharmaceutical substance and an amphiphilic material) to be formed in order to solubilise the pharmaceutical substance. The formation of a hydrophobic ion-pair complex is an essential part of the process

described in Manning *et al.*, and this, combined with the fact that the amphiphilic material used in the hydrophobic-ion pair complex is present in the material that is ultimately precipitated, would, we submit, provide no motivation to the person of ordinary skill in the art to modify the Manning *et al.* process. The person of ordinary skill in the art wanting to prepare a precipitate of a pharmaceutical active without the presence of the amphiphilic material in the product would not be motivated to modify the Manning *et al.* process to leave out the amphiphilic material, since there would be no reasonable expectation that such a modification would be successful. Moreover, there is good reason to avoid including amphiphilic ions given regulatory approvals which would be required for incorporation of them into a pharmaceutical.

Prior art must teach/suggest all the recited claim limitations

In relation to Merrified *et al.*, we respectfully submit that the process described in the document does not teach or suggest all of the features recited in claim 1 of the present application. As outlined above, Merrified *et al.* provides no teaching or suggestion that the precipitation of the substance of interest occurs at the point of contact of the fluid streams, as is required by claim 1 of the present application. We direct the Examiner to our discussion above, under the heading "Motivation to combine documents".

In relation to Manning *et al.*, we submit that the process described in the document does not teach or suggest all of the features recited in claim 1 of the present application. The solubilisation process described in Manning *et al.* requires that a hydrophobic-ion pair complex be formed between the pharmaceutical substance and an amphiphilic material. The amphiphilic material forms a complex with the pharmaceutical substance which results in the complex dissolving in the organic solvent to form a single liquid phase (see column 5, lines 4-13 of Manning *et al.*), whereas the pharmaceutical substance alone has limited solubility in the organic solvent (see column 4, lines 53-55 and column 6, lines 25-29 of Manning *et al.*).

Claim 1 as filed, of the present application requires that the dense gas includes "...(a) an antisolvent and (b) a modifying agent which modifies the polarity of the antisolvent."

If one assumes, for the sake of argument, that the amphiphilic material in the Manning *et al.* process is acting as a modifying agent, the amphiphilic material is actually altering the properties of the pharmaceutical substance and would not be altering the polarity of the antisolvent, as is required by claim 1 of the present application. Indeed, the amphiphilic material is not added to the antisolvent in any event. Therefore, the Office Action's allegation that "... there is nothing within the language of the instant claims that bars the use of such complexes" (i.e.; hydrophobic ion pair complexes), is, we respectfully submit, incorrect.

Further, in Manning *et al.*, when the true, homogeneous solution containing the hydrophobic-ion pair complex is subjected to a precipitation process, the amphiphilic material is actually present in the precipitated material (see column 11, lines 21-23), unlike the product of the process claimed in claim 1 of the present application where the modifying agent evaporates when the product is precipitated.

We therefore submit that claim 1 of the present invention application is not obvious in light of Manning *et al.* for at least the reasons stated above. Accordingly, for at least the reasons given above, Applicants respectfully request that the rejection of claims 1-24 and 27-29 under 35 U.S.C. §103 be withdrawn.

Conclusion

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

No fee is deemed necessary with the filing of this paper. However if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

Date: February 6, 2006

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